UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY 100 1918·2018

Morning Brief : Scientific Review

03 July 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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Content

Statistics
Systematic review: pathology

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REPORT ON WEEKLY DEATHS IN SOUTH AFRICA

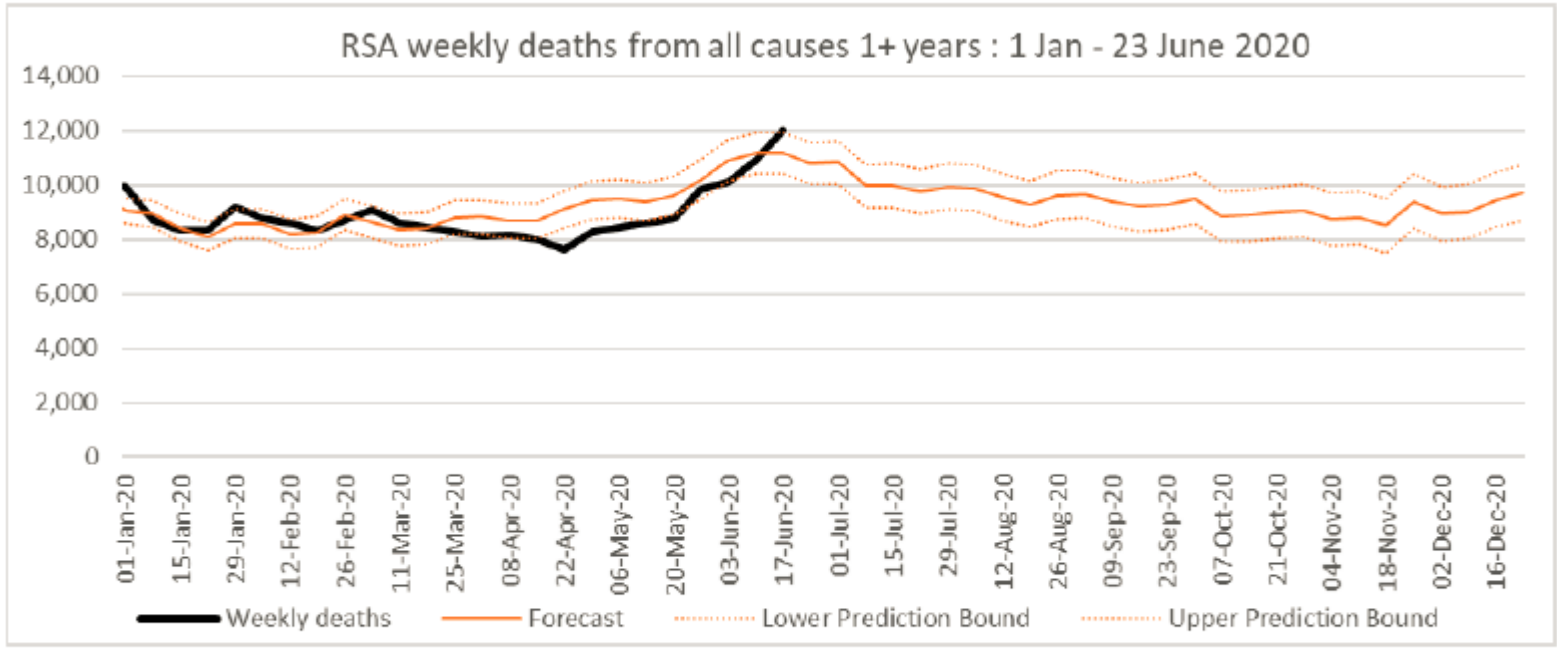
1 JANUARY – 23 JUNE 2020 (WEEK 25)

Debbie Bradshaw, Ria Laubscher,
Rob Dorrington, Pam Groenewald, Tom Moultrie

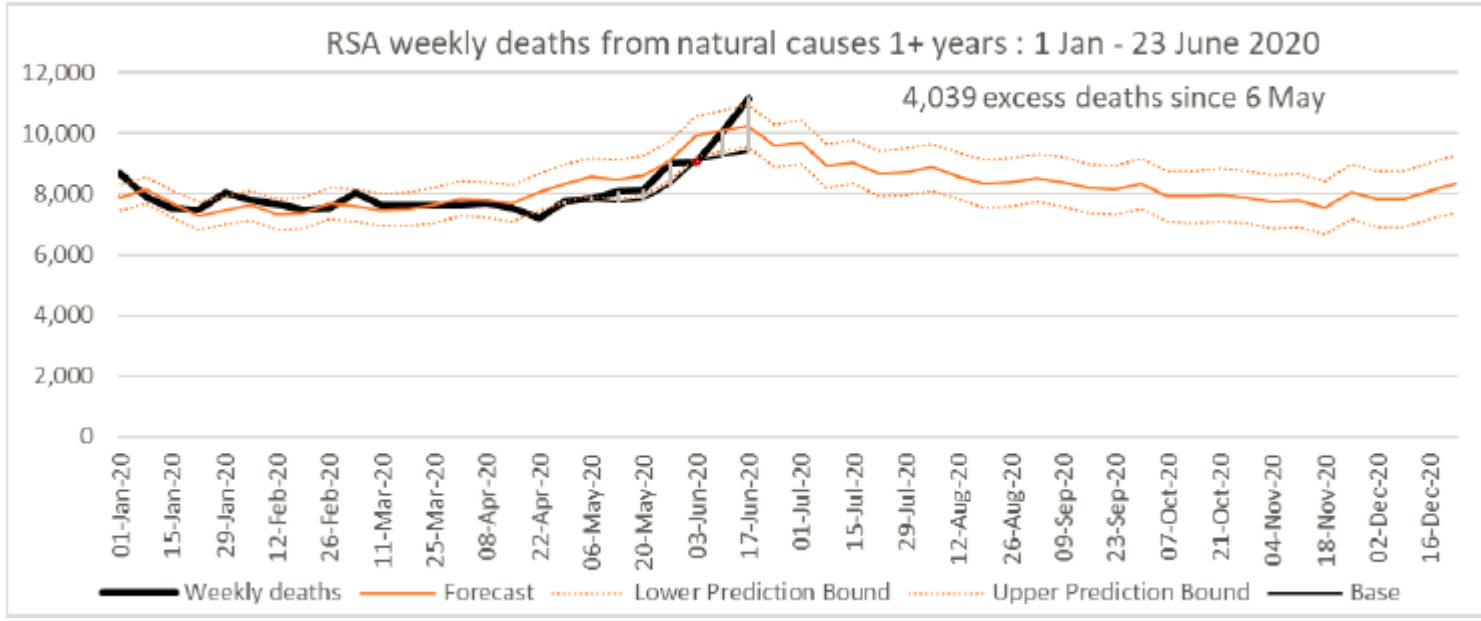
Burden of Disease Research Unit
South African Medical Research Council
30 June 2020

saMRC advancinglife

UCT Centre for Actuarial Research



Numbers have been scaled to the estimated actual number of death and for the last week has been adjusted for delayed registrations



Weekly deaths : Excess deaths

Region	Excess deaths 6 May-23 June
South Africa	4,039
Province	
Eastern Cape	1,421
Free State	69
Gauteng	399
KwaZulu-Natal	351
Limpopo	95
Mpumalanga	-
Northern Cape	-
North West	-
Western Cape	2,366
Metropolitan Municipality	
Buffalo City	202
City of Cape Town	2,167
Ekhuruleni	148
Ethikweni	-
Johannesburg	115
Mangaung	-
Nelson Mandela Bay	455
City of Tshwane	202

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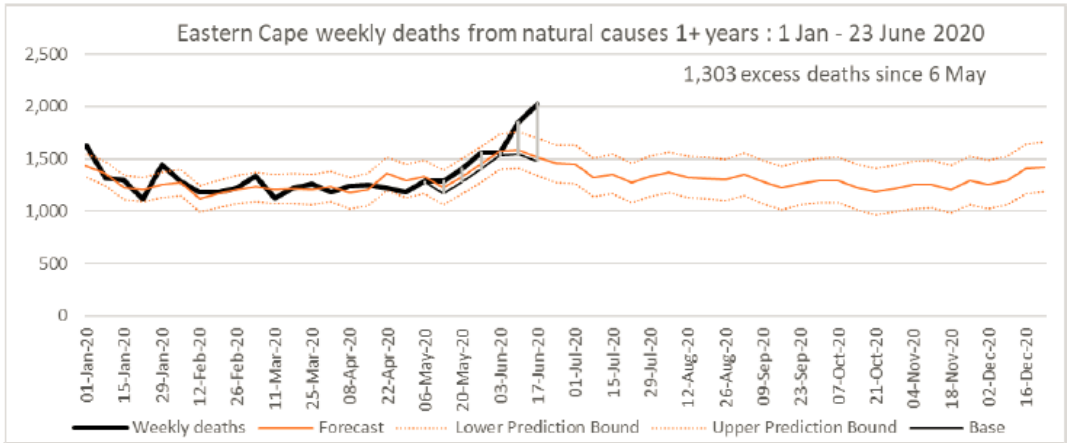

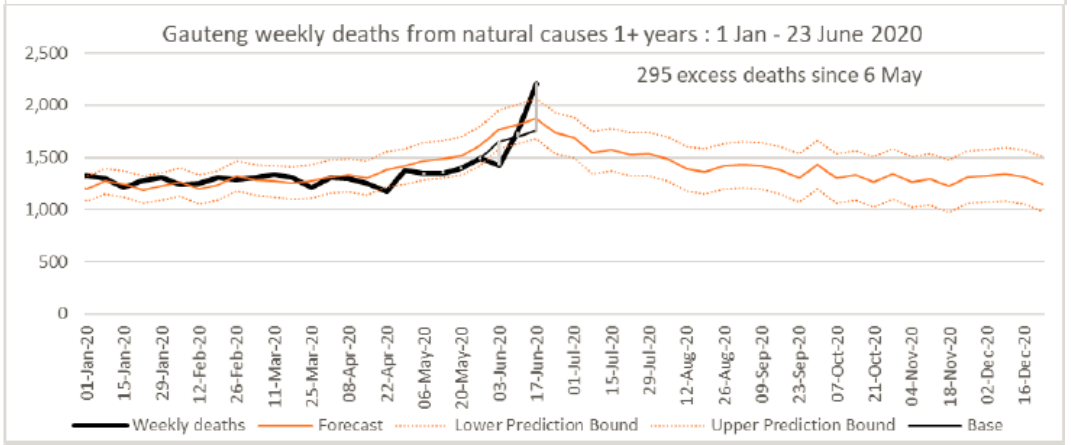

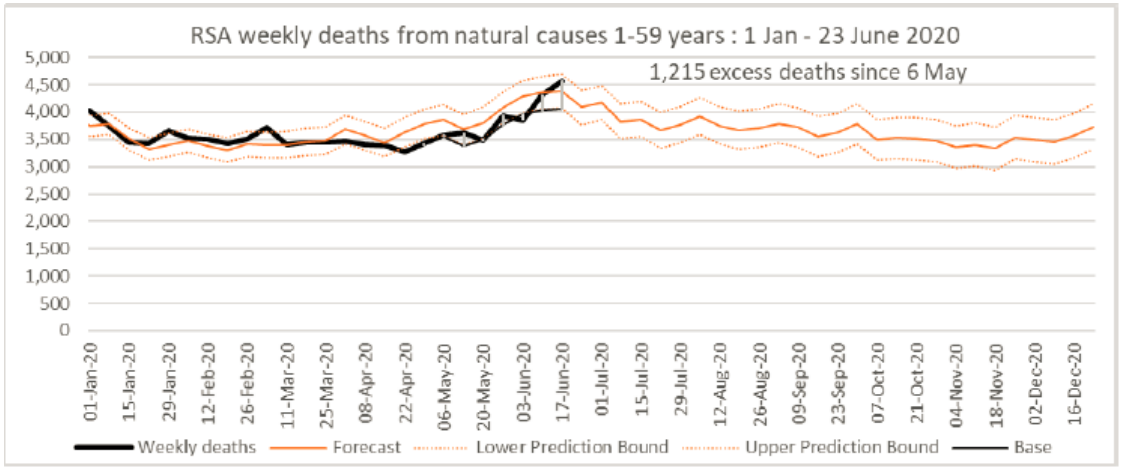

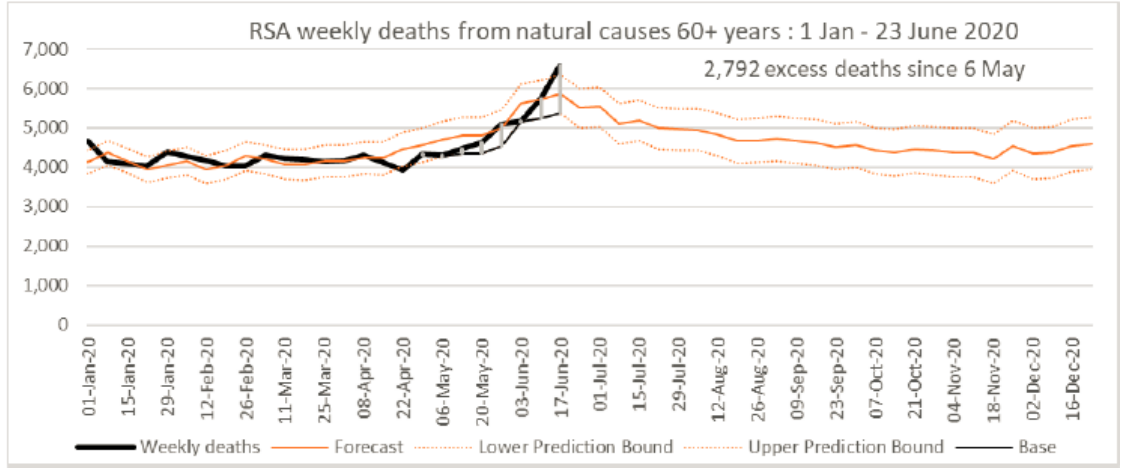

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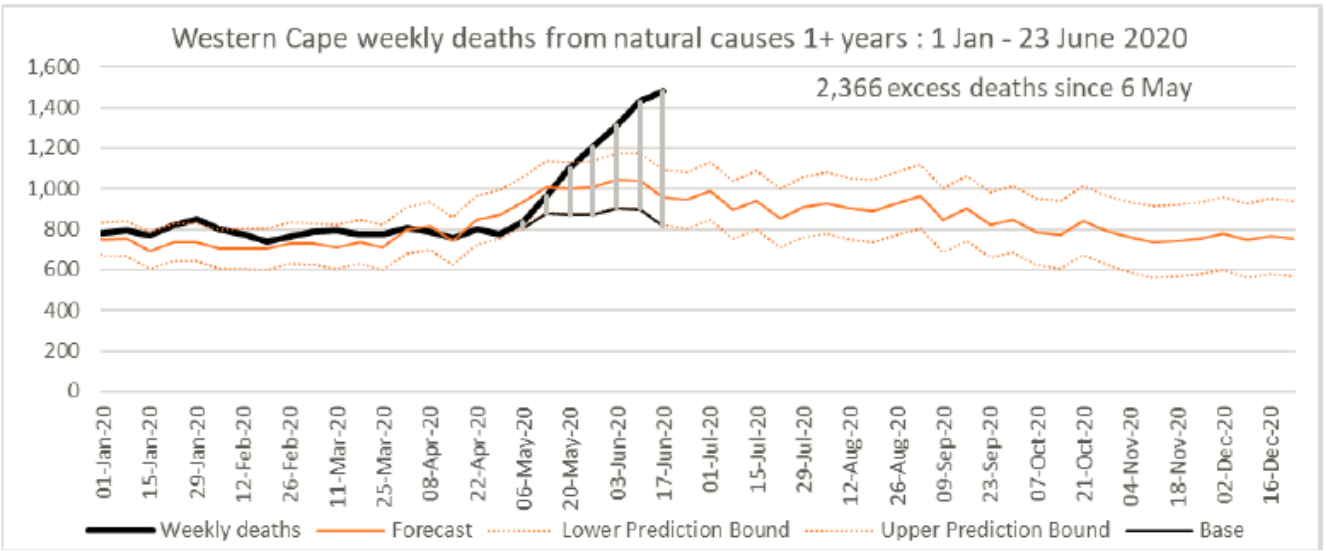

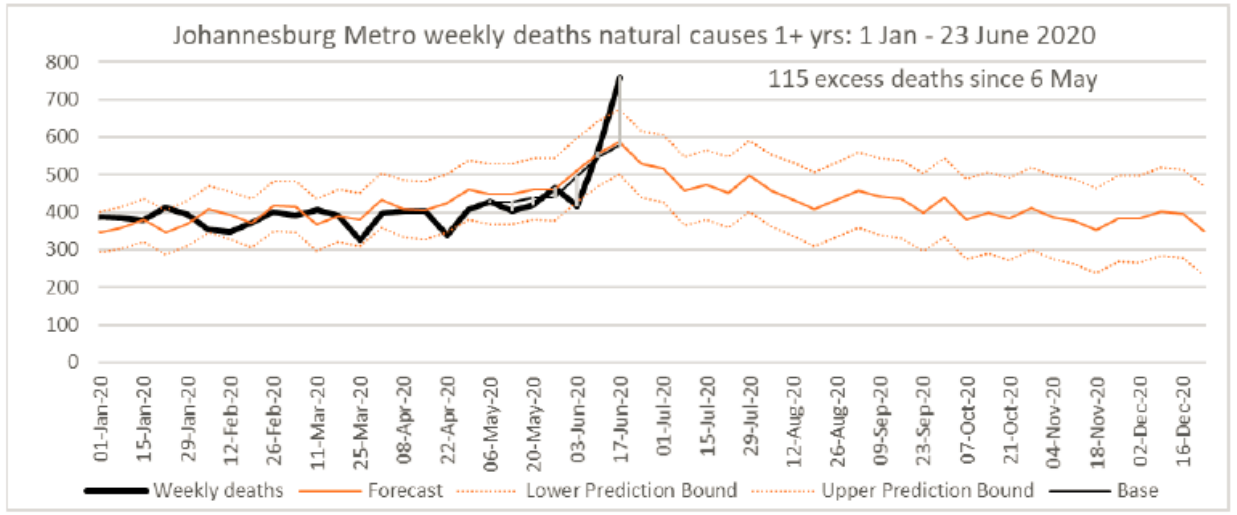

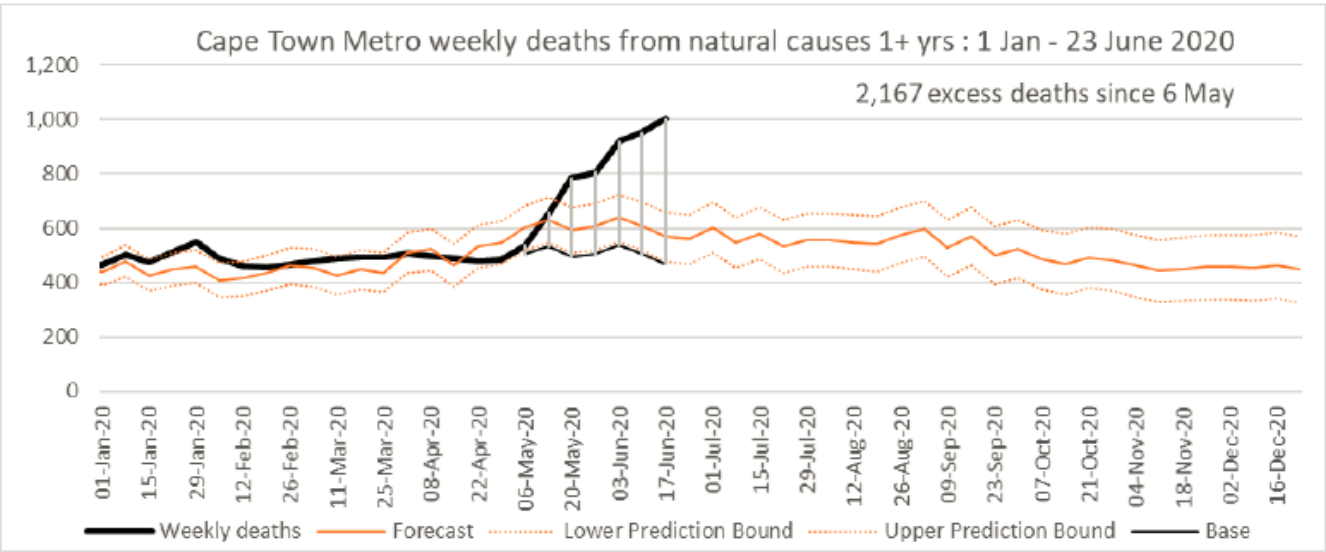

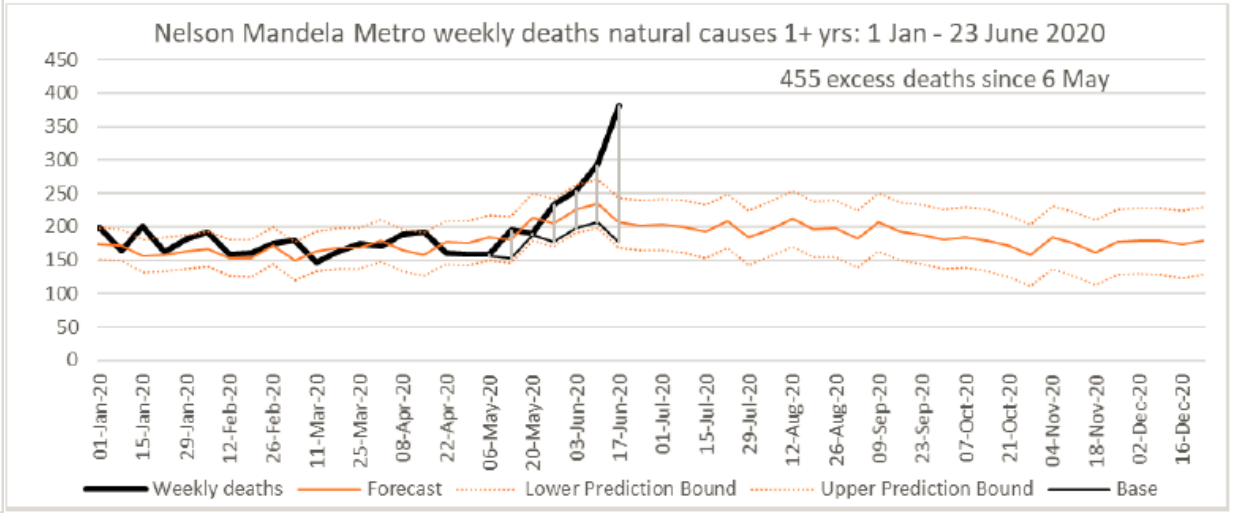

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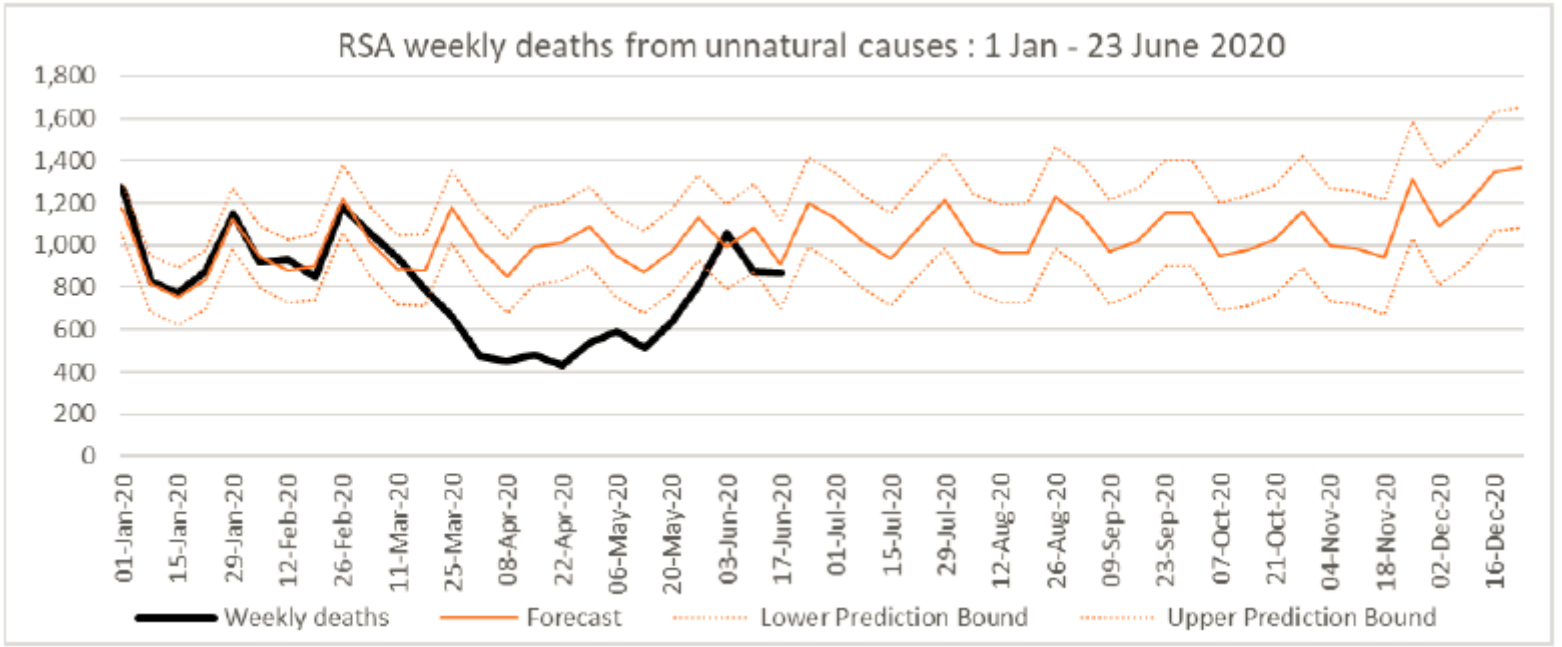


A systematic review of pathological findings in COVID-19:
a pathophysiological timeline and possible mechanisms of disease progression

Samuel B. Polak ● Inge C. Van Gool ● Danielle Cohen ● Jan H. von der Thüsen ● Judith van Paassen

Modern Pathology

https://doi.org/10.1038/s41379-020-0603-3

Presented by Stephanus Malherbe MD, PhD.

Molecular Biology Clinical Research Unit

What was the aim?

- Systematically review published case reports and case series in order to increase our understanding of COVID-19 pathophysiology by constructing a timeline and correlating histopathological findings with clinical stages of COVID-19.

Why?

- To put together all the emerging data to understand COVID-19 pathology and provide clues as to
  - Why some interventions may work, and getting the timing right
  - Why some groups are more at risk
  - Why the high mortality in severe disease
  - Prognostic markers
- Try to get figure out measurable indicators of underlying pathology

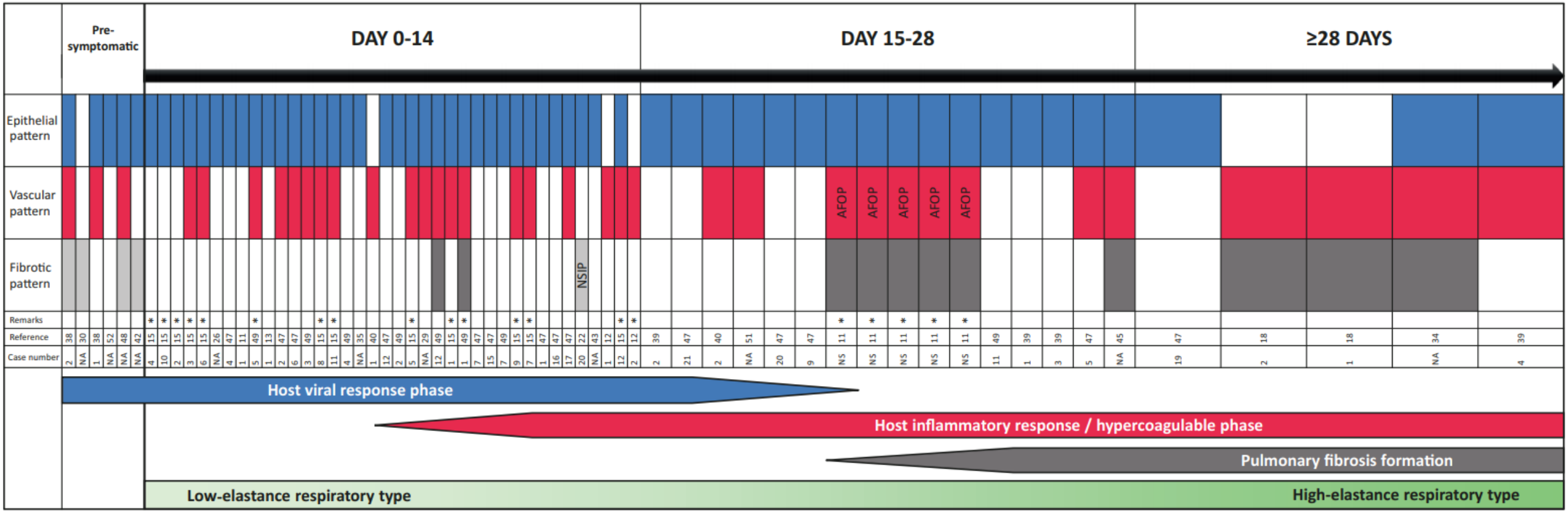
How did they do it?

- Systematic screening of large databases looking at title and abstract reviewed by two readers, a third reader used as tie breaker to see if on topic
- Quality check of using criteria
  - reporting of clinical data per case,
  - reporting of microscopic evaluation per case, and reporting of macroscopic evaluation per case.
- Extracted data, reported per organ system

What did they find

- 42 cases reports and series
- In 21 of the 42 articles (50%), we were able to extract time between the onset of symptoms and tissue collection and lung histopathological evaluations for individual patients; these 21 articles were therefore included in the timeline synthesis
- 198 patients with COVID-19 (n=43 full autopsy, n=91 partial autopsy; n=4 antemortem pneumonectomy; n=13 antemortem partial lung resections; n=3 placenta; n=1 small intestine resection; n=15 antemortem biopsy, n=28 postmortem biopsy
- 74% male
- Median age 67
- Co-morbidities included Hpt (49%), CVD (28%) DM (24%)

Lung pathology



Stages of Respiratory pathology

1. Epithelial pattern, ascribed to host-viral interaction from pre-symptomatic phase into first 14 days.
2. Host-inflammatory pattern and hypercoagulation from 7 – 28 days
3. Fibrotic phase from day >20

Notable overlap, so timelines alone not adequate

Epithelial phase

- In the first two weeks the lungs show low elastin type respiratory disease and normal weight lungs
- Diffuse alveolar or hyaline membrane damage; changes in pneumocytes, Macrophages in alveoli, Lymphocytes and plasma cells interstitial, viral changes
  - Associated with good lung compliance,
  - Dysregulated pulmonary vasoconstriction, low V/Q ratio, low lung recruitability
  - Ground glass opacity only on radiography
  - Viral DNA still detectable

Vascular or host-immune response stage

- High elastin type respiratory disease, oedematous lungs with increased weight. Driven by strong pro-inflammatory response (mixed innate, adaptive)
- Capillary congestion, micro-thrombi, interstitial and alveolar oedema, capillary changes, necrosis
- Can occur shortly after symptom onset, more frequent after 7 days
  - Poor compliance, high V/Q pattern and high recruitability
  - Consolidation or edema on radiography
  - No evidence of pulmonary embolism on those that had CT

  - Coagulation tests not described in enough cases for evaluation

Fibrotic stage

- After 3 weeks (timeline fairly consistent)
- NOT associated with mechanical ventilation
- Interstitial fibrous changes (fibroblast hyperplasia, fibrosis, collagen deposition.

Notable findings in other organs

- Cardiac
  - Pre-existing disease common
  - Infrequent occurrences included interstitial inflammation and mild edema, lymphocytic myocarditis
- Liver
  - Mild steatosis, patchy hepatic necrosis, Kupffer cell hyperplasia
- Renal
  - Hypertensive changes common
  - Acute tubular injury, renal vascular changes associated with fibrin

- No thrombosis is cardiac or hepatic vasculature, (hyper coagulation lung specific?)

Author summary

- Effective treatment at different stages likely to differ
  - Antivirals most likely to (only) help in first stage (Perhaps why trials of such treatments failed if started after severe disease set in)
  - Vascular stage require anti-inflammatory, anticoagulant, and anti-compliment.
  - Fibrotic stage may benefit from biologicals or anti-fibrotic compounds

- Challenging to precisely work out underlying pathology in practice
- Inflammatory and imaging markers may help, but need more evaluation by multidisciplinary teams to more directed therapies

Impressions

- High quality review presenting a good overview of the natural history of COVID 19 disease
- Admiral job of putting together pathology and clinical findings
- As review, no new knowledge (perhaps that hyper coagulation seemed to disproportionately affect lungs, but not other organ)

This summary was prepared by Dr Fanie Malherbe as part of the daily brief to the TBH ICU team.